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Impact of hypertension on the diagnostic accuracy of coronary angiography with computed tomography

Lars Husmann · Hans Scheffel · Ines Valenta · Tiziano Schepis · Oliver Gaemperli · Ursina Aepli · Patrick T. Siegrist · Sebastian Leschka · Lotus Desbiolles · Paul Stolzmann · Borut Marincek · Hatem Alkadhi · Philipp A. Kaufmann

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Abstract *Objective* Hypertension induces coronary artery disease (CAD) and progression of arterial wall calcification. As coronary calcifications may cause artefacts in 64-slice computed tomography coronary angiography (CTCA), we sought to determine the diagnostic accuracy of CTCA in patients with and without arterial hypertension. *Methods* Eighty-five consecutive patients with suspected CAD underwent CTCA, calcium-scoring and conventional coronary angiography, and were grouped as hypertensive (28 women, 31 men, mean age 65 ± 9 years, age range 49–82 years) or normotensive patients (10 women, 16 men, mean age 62 ± 11 years, age range 39–77 years). On an intention-to-diagnose-basis, no coronary segment was excluded and non-evaluative segments were rated as false positive. *Results* Per-patient sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in the hypertensive group were 91.4, 83.3, 88.9, and 86.9%, while the respective values in the normotensive group were 100, 78.9, 63.6, and 100% ($P = 0.42$, 0.71, 0.05, and 0.15). In the hypertensive group the prevalence of CAD was 59% and the mean calcium-score was 256; respective values in the normotensive group were 27% and 69, ($P < 0.01$, and < 0.05 vs. hypertensives). *Conclusions* Although hypertensives have significantly higher coronary calcifications, sensitivity and specificity are comparably high as in normotensives. The prevalence of CAD is higher in hypertensives and brings about a trend towards a lower NPV and a higher PPV.

Keywords Coronary artery disease · Imaging · Hypertension · Diagnostic accuracy · Prevalence · Coronary angiography · 64-slice computed tomography

Abbreviations

CAD	Coronary artery disease
CTCA	Computed tomography coronary angiography
CCA	Conventional coronary angiography

Introduction

Computed tomography coronary angiography (CTCA) has been shown to reliably detect coronary artery disease (CAD) [1–12]. As a non-invasive tool its clinical role has been outlined to obviate the need for conventional coronary angiography (CCA) in patients

L. Husmann · I. Valenta · T. Schepis · O. Gaemperli · U. Aepli · P. T. Siegrist · P. A. Kaufmann (✉)
Cardiovascular Center, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland
e-mail: pak@usz.ch

L. Husmann · H. Scheffel · S. Leschka · L. Desbiolles · P. Stolzmann · B. Marincek · H. Alkadhi
Institute of Diagnostic Radiology, University Hospital Zurich, Zurich, Switzerland

P. A. Kaufmann
Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

with a low to intermediate pre-test probability, whose symptoms, inconclusive electrocardiograms or equivocal stress tests require specific testing [13–15].

Hypertensive patients are more prone to CAD as compared with normotensive patients [16, 17] and an aggravating effect of hypertension on the progression of arterial wall calcification has been well established in several studies [18–20]. Coronary calcifications, however, may often cause blooming artefacts in CTCA, leading to overestimation of lesion severity [21]. This may lead to false positive ratings, resulting in lower specificity and positive predictive value (PPV).

The purpose of this study was to prospectively determine the diagnostic accuracy of 64-slice CTCA in patients with unknown CAD and compare groups of patients with and without hypertension.

Methods

Patients

Eighty-five consecutive patients (38 women, 47 men; mean age 64.4 ± 9.4 years; age range 39–82 years) scheduled for CCA were prospectively enrolled and underwent an additional CTCA if none of the following exclusion criteria were present: hypersensitivity to iodinated contrast agent, renal insufficiency (creatinine levels >150 μmol/l), non-sinus rhythm, or hemodynamic instability. Patients were referred due to suspected CAD based on symptoms such as dyspnoe ($n = 20$), typical angina pectoris ($n = 31$), atypical chest pain ($n = 18$), or to preoperatively rule out CAD ($n = 16$). They were categorized in groups with and without hypertension, with hypertension defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg [22], and/or patients with known arterial hypertension currently normotensive at antihypertensive medication.

The study protocol was approved by the local ethics committee and written informed consent was obtained from all patients.

CT data acquisition and post-processing

All CT examinations were performed on a 64-slice CT scanner (Somatom Sensation 64, Siemens Medical Solutions, Forchheim, Germany). CT scans were performed during inspiration at breath hold using the following scanning parameters: detector collimation of 32 × 0.6 mm, slice acquisition 64 × 0.6 mm by means of a z-flying focal spot, pitch of 0.2, gantry rotation time 330 ms, tube voltage of 120 kV and an effective tube-current time product of 650 mAs (CTCA) and 60 mAs (calcium scoring). All patients received a single dose of 2.5 mg isosorbiddinitrate sublingual (Isoket, Schwarz Pharma, Monheim, Germany) 2 min prior to the scan. In addition, intravenous metoprolol (5–20 mg) (Beloc, AstraZeneca, London, UK) was administered prior to the CTCA examination to achieve a target heart rate <70 beats per minute (bpm), if necessary. For CTCA, 80 ml of iodixanol (Visipaque 320, 320 mg/ml, GE Heathcare, Buckinghamshire, UK) at a flow rate of 5 ml/s followed by 30 ml saline solution was injected into an antecubital vein via an 18-gauge catheter. Bolus tracking was performed with a region of interest placed into the ascending aorta, and image acquisition was automatically started 5 s after the signal density reached a predefined threshold of 100 Hounsfield units.

CT image reconstruction and analysis

Non-enhanced CT were reconstructed at 60% of the R-R interval using non-overlapping slices (thickness 3.0 mm; reconstruction kernel B35). Contrast-enhanced CT angiograms were retrospectively reconstructed throughout the entire cardiac cycle in 5% steps of the R-R interval. CTCA images were reconstructed with a slice thickness of 1.0 mm and an increment of 0.8 mm, using a medium-soft and a sharp tissue convolution kernel (B30f). In case of vessel wall calcifications, additional images were reconstructed using a sharp-tissue convolution kernel (B46) and preferably analyzed using a bone window setting (window width: 1500 HU; window level: 500 HU) to compensate for blooming artifacts. All images were transferred to an external workstation (Leonardo, Siemens Medical Solutions).

Calcifications were quantified with dedicated scoring software (Syngo CaScore, Siemens Medical Solutions) using the Agatston method [23].

For analysis of CTCA data, coronary arteries were segmented as suggested by the American Heart Association [24]: The right coronary artery (RCA) was defined to include segments 1–4, the left main artery (LM) and the left anterior descending artery

(LAD) to include segments 5–10, and the left circumflex artery (CX) to include segments 11–15. The intermedial artery was designated as segment 16, if present. All segments with a diameter of at least 1.5 mm at their origin were included.

First, one reader semi-quantitatively assessed the overall image quality in the best reconstruction interval on a 5-point scale, based on a previously published score [25, 26] (1, no artifacts; 2, mild artifacts; 3, moderate artifacts; 4, severe artifacts; 5 non-evaluative), and determined the reconstruction interval with the best image quality. Images in the best reconstruction interval were evaluated and classified by two independent readers using axial source images, multi-planar reformations, and thin-slab maximum intensity projections on a per-segment basis. Both readers visually assessed all coronary artery segments for the presence of significant stenoses, defined as narrowing of the coronary luminal diameter $\geq$50%. For any disagreement in data analysis between the two observers, consensus agreement was achieved. Diagnostic accuracy of CTCA was determined on an "intention-to-diagnose"-basis; no coronary segment was excluded; non-evaluative segments were rated as stenosed, as previously suggested [27].

Conventional coronary angiography

CCA was performed according to standard techniques and multiple views were recorded for further analysis. The angiograms were evaluated by two experienced observers who were aware of the patients' clinical history but blinded to the results from CTCA. Coronary artery segments were defined as mentioned above [24], and analysis was performed in all vessels with a luminal diameter of at least 1.5 mm, excluding those vessels distal to complete occlusions. Each vessel segment was scored as being significantly stenosed, defined as a diameter reduction of $\geq$50%.

Statistical analysis

Quantitative variables were expressed as mean $\pm$ standard deviation and categorical variables as frequencies, median (25th, 75th percentiles), or percentages.

Kappa statistics were calculated for inter-observer agreements for assessment of significant coronary artery (patient-, vessel-, and segment-based) stenoses.

Sensitivity, specificity, PPV, negative predictive value (NPV) and accuracy in the identification of stenoses were assessed on a per-segment, per-vessel, and per-patient basis by using cross tables. CCA was considered the standard of reference.

Differences between the two groups regarding diagnostic performance were tested for significance by using χ^2-tests for comparison of cross tables. For further comparison, Student's t-tests for independent samples were performed for the variables: age, heart rate, heart rate variability, blood pressure and body mass index (BMI). Mann–Whitney-*U*-tests were performed for image quality, best reconstruction interval, and calcium-score. χ2-tests were performed for gender, symptoms, diabetes, smoking, dyslipidemia, prevalence of CAD, and true positive, true negative, false positive and false negative findings. A *P*-value of <0.05 was considered to indicate statistical significance. SPSS software (SPSS 15.0, Chicago, ILL, USA) was used for statistical testing.

Results

CCA and CTCA were successfully performed in all 85 patients within 8 $\pm$ 16 days. The study population consisted of 59 hypertensive (69%) and 26 normotensive patients (31%). As a consequence of the study design blood pressure was significantly higher in hypertensives than in normotensives, despite antihypertensive treatment (Table 1). Forty-one patients (48%) were on oral beta-adrenoreceptor antagonist medication as part of their anti-hypertensive medication, additional intravenous metoprolol prior to the CT examination was administered in 7 (8%) patients. Baseline characteristics of the entire study population and within both groups are given in Table 1; notably, the coronary calcium-score was significantly higher in the group of hypertensive patients, as compared to normotensive patients, while gender, age, BMI, and overall image quality did not differ.

In 85 patients, a total of 339 vessels (1 missing left main artery) and 1151 coronary artery segments with a diameter $\geq$1.5 mm were evaluated (of the 209 missing segments 135 were missing due to anatomical variants and 74 had a diameter less than 1.5 mm at their origin). Thirteen segments (1.1%) were rated not evaluative in CTCA due to motion artifacts and were subsequently scored as "false positive" on an

Table 1 Patient demographics

	All patients	Hypertensive patients	Normotensive patients	Significance (*P*=)
Number of patients (*n*)	85	59	26	
Female/male (*n*)	38/47	28/31	10/16	0.44
Age (years)	64.4 ± 9.4 (39–82)	65.3 ± 8.6 (49–82)	62.2 ± 10.9 (39–77)	0.16
BMI (kg/m^2)	23.1 ± 4.0 (13.3–35.8)	23.1 ± 3.9 (14.2–34.0)	23.3 ± 4.5 (13.3–35.8)	0.86
Dyslipidemia (*n*)	35	28	7	0.08
Diabetes (*n*)	15	12	3	0.33
Smoking (*n*)	36	26	10	0.63
Systolic BP (mmHg)	136 ± 19 (100–190)	142 ± 18 (100–190)	122 ± 12 (101–139)	<0.001
Diastolic BP (mmHg)	79 ± 12 (45–110)	83 ± 10 (63–110)	70 ± 10 (45–86)	<0.001
No symptoms (*n*)	16	9	7	0.21
Typical angina pectoris (*n*)	31	22	9	0.70
Atypical chest pain (*n*)	19	13	5	0.77
Dyspnoea (*n*)	20	15	5	0.54
HR at CTCA (bpm)	63.3 ± 9.1 (46–90)	63.1 ± 9.7 (46–90)	63.8 ± 7.9 (48–76)	0.78
HR variability at CTCA (bpm)	4.3 ± 4.4 (0.5–22.2)	4.6 ± 4.8 (0.8–22.2)	3.7 ± 3.3 (0.5–14.8)	0.39
Best CTCA recon. interval 30,35,40,55,60,65,70%	60 (60,70) 5,7,3,3,41,19,7	60 (60,70) 4,6,3,2,28,12,4	60 (60,70) 1,1,0,1,13,7,3	0.13
Overall CTCA image quality score 1,2,3,4,5	2 (1,4) 30,30,17,8,0	2 (1,4) 19,22,13,5,0	2 (1,4) 11,8,4,3,0	0.53
Coronary calcifications (*n*)	68	49	19	0.29
Coronary calcium-score	156 (5,1908)	256 (45,1908)	69 (0,1025)	<0.05

Quantitative variables are expressed as mean ± standard deviation (range); categorical variables are expressed as frequencies, or median (25th, 75th percentiles); BMI: body mass index; BP: blood pressure; CTCA: computed tomography coronary angiography; HR: heart rate; recon.: reconstruction

intention-to-diagnose-basis; i.e. 3/798 segments (0.4%) in the hypertensive group of patients and 10/353 segments (2.8%) in the normotensive group.

Diagnostic performance of CTCA

A total of 112 coronary artery stenoses with a diameter narrowing of more than 50% in diameter were identified with CCA in 42/85 patients (49%). Coronary artery stenosis was most often found in the LAD (29/85; 34%) and the CX (29/85; 34%), followed by the RCA (23/85; 27%), and the LM (1/84; 1%). Single-vessel disease was present in 16/85 (19%), 2-vessel disease in 13/85 (15%), and 3-vessel disease in 13/85 (15%). Significant CAD was excluded in 43/85 patients (51%). The prevalence of CAD was significantly higher in the group of hypertensive patients (59% vs. 27%, $P < 0.01$) (Table 2).

Kappa values for inter-observer agreement for coronary artery stenosis detection with CTCA were 0.91, 0.69, and 0.57 (patient-, vessel-, and segment-based) indicating a moderate to excellent agreement.

The patient-based analysis revealed that CTCA correctly ruled out CAD in 35/43 (81%) patients (hypertensive patients (HP) 20/24, 83%; normotensive patients (NP) 15/19, 79%; with a no significant difference between the groups: $P = 0.72$) and correctly identified patients with significant stenosis in 39/42 (93%) patients (HP 32/35, 91%; NP 7/7, 100%; $P = 0.42$). Eight of 43 (19%) patients without CAD (HP 4/24, 17%; NP 4/19, 21%; $P = 0.72$) were falsely rated to have CAD and 3/42 (7%) patients with CAD (HP 3/35, 9%; NP 0/7, 0%; $P < 0.42$) were falsely rated to have no CAD.

The overall diagnostic performance of CTCA, and within both groups on a patient-, vessel-, and segment-based analysis is presented in Table 2 and

Table 2 Diagnostic accuracy of CTCA

	All patients	Hypertensive patients	Normotensive patients	Significance (*P*=)
Number of patients	85	59	26	
Number of vessels	339	236	103	
Number of segments	1151	798	353	
Prevalence of CAD (one-, two-, three-vessel)	42 (16, 13, 13)	35 (14, 12, 9)	7 (2, 1, 4)	<0.01 (0.08, 0.05, 0.98)
Patient-based analysis				
Sensitivity	92.9% (80.5–98.5)	91.4% (76.9–98.2)	100% (NA)	0.42
Specificity	81.4% (66.6–94.6)	83.3% (62.6–95.3)	78.9% (54.4–93.9)	0.71
PPV	82.9% (69.2–92.4)	88.9% (73.9–96.9)	63.6% (30.8–89.1)	0.05
NPV	92.1% (78.6–98.3)	86.9% (66.4–97.2)	100% (NA)	0.15
Accuracy	87.1% (78.0–93.4)	88.1% (77.1–95.1)	84.6% (65.1–95.6)	0.66
Vessel-based analysis				
Sensitivity	90.2% (81.7–95.7)	89.2% (79.1–95.6)	94.1% (71.3–99.9)	0.55
Specificity	92.6% (88.7–95.5)	92.4% (87.4–95.9)	93.0% (85.4–97.4)	0.86
PPV	79.6% (69.9–87.2)	81.7% (70.7–89.9)	72.7% (49.8–89.3)	0.36
NPV	96.8% (93.7–98.6)	95.8% (91.5–98.3)	98.8% (93.3–99.9)	0.21
Accuracy	92.0% (88.6–94.7)	91.5% (87.2–94.8)	93.2% (86.5–97.2)	0.60
Segment-based analysis				
Sensitivity	80.4% (71.8–87.3)	81.6% (71.9–89.1)	76.0% (54.9–90.6)	0.53
Specificity	96.2% (96.2–97.2)	95.8% (94.0–97.1)	96.9% (94.4–98.5)	0.36
PPV	69.2% (60.5–77.0)	70.3% (60.4–78.9)	65.5% (45.7–82.1)	0.62
NPV	97.9% (96.8–98.6)	97.7% (96.3–98.7)	98.1% (96.0–99.3)	0.65
Accuracy	94.6% (93.2–95.9)	94.2% (92.4–95.8)	95.4% (92.7–97.4)	0.39

Values for diagnostic accuracy in parentheses represent 95% confidence intervals; CAD: coronary artery disease; NA: not available; NS: not significant; NPV: negative predictive value; PPV: positive predictive value

Fig. 1. There are trends towards a higher PPV ($P = 0.05$) and a lower NPV ($P = 0.15$) in hypertensive patients as compared to normotensive patients. Sensitivity and specificity do not differ between both groups.

Discussion

The present study is the first to establish the value of 64-slice CT to assess CAD in hypertensive patients. The results demonstrate that although hypertensives have significantly higher coronary calcifications, which may impair diagnostic accuracy of CTCA [3], sensitivity and specificity do not differ compared to normotensives. Furthermore, as prevalence of CAD is higher in hypertensives, a trend towards a higher PPV and a lower NPV is documented in this patient group.

The fact, that hypertension is a major risk factor for CAD [16, 17] is fully in line with the results of our study population, showing that the prevalence of CAD in hypertensive patients is significantly higher compared to normotensive patients. It is also known, that the prevalence of a disease affects the diagnostic performance of a test, in a way that the PPV increases and the NPV decreases when the prevalence increase, while sensitivity and specificity are generally not affected (Bayesian theorem). With CTCA the Bayesian theorem can be easily followed with our results and the results of previous CTCA studies: So far the study population with the highest prevalence of CAD was presented by Ehara et al. [8] with 88%, while the patient population with the lowest prevalence was presented by Ropers et al. [9] (31%). The PPV was 98% by Ehara et al. and 83% by Ropers et al. [9], comparable to the high PPV in our hypertensive group (PPV: 89%; prevalence 59%) and the lower PPV in

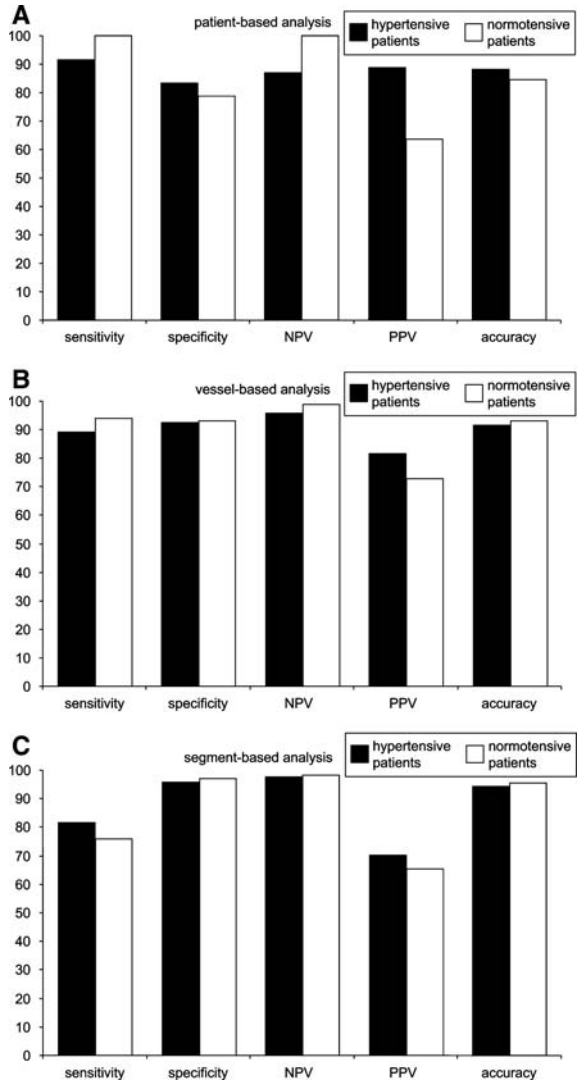

Fig. 1 Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy of CTCA in comparison to the reference standard CCA for the detection of significant coronary artery disease in hypertensive and normotensive patients on a patient- (**a**), vessel- (**b**), and segment-based analysis (**c**)

our normotensive group (PPV: 64%; prevalence 27%). Again fully in line with the Bayesian theorem, the NPV was lower in the high prevalence study [8] as compared to the low prevalence study [9] (86% vs. 98%), and similarly, lower in our hypertensive group than in our normotensive group (87% vs. 100%).

Hypertension is associated with a progression of arterial wall calcification [18–20], which was underlined by a significantly higher coronary calcium-score in our hypertensive patient group. As coronary calcifications have been suspected to lead to blooming artefacts and subsequent overestimations of lesions with false positive ratings and lower specificity in CTCA [21], Raff et al. [3] found sensitivity of CTCA to increase with increasing calcium-score and specificity to decrease with increasing calcium-score. In order to compensate this shortcoming of CTCA the use of a sharp tissue-convolution kernel for the assessment of calcified coronary lesions has been introduced [28], to reduce the blooming artifacts that occur at the edges of calcified plaques; however a significant increase in image noise has to be accepted with the use of a sharp kernel [29]. In the present study we have evaluated all calcified lesions with a sharp-tissue convolution kernel, and no differences in sensitivity and specificity were found between the hypertensive patients with a high calcium-load and the normotensive patients with a low calcium-load (Fig. 2). Therefore, we believe that the use of a sharp tissue convolution kernel for the evaluation of calcified lesions can be considered adequate. Our values are therefore not comparable to those by Schuijf et al. [30], who evaluated the diagnostic performance of 4- and 16-slice CT in hypertensive patients.

Study limitations

χ^2-tests for comparison of diagnostic performance on a per-vessel and per-segment-basis must be regarded as an approximation because of data clustering. However, adequate statistical testing could not be applied because of small group sizes, and therefore further studies with larger patient populations are required to confirm the results of our study.

Furthermore, the blinded separate analysis of CCA and CTCA may have affected the agreement on a segment based analysis, as assignment of segments may have introduced a subjectivity bias. However, high kappa values indicate an excellent inter-observer agreement on the clinically per patient level.

Finally, our study was performed using 64-slice CT and not using most recent dual-source CT scanner technology [11].

Perspectives

The amount of false positive and false negative ratings by CTCA is low in hypertensives and does not

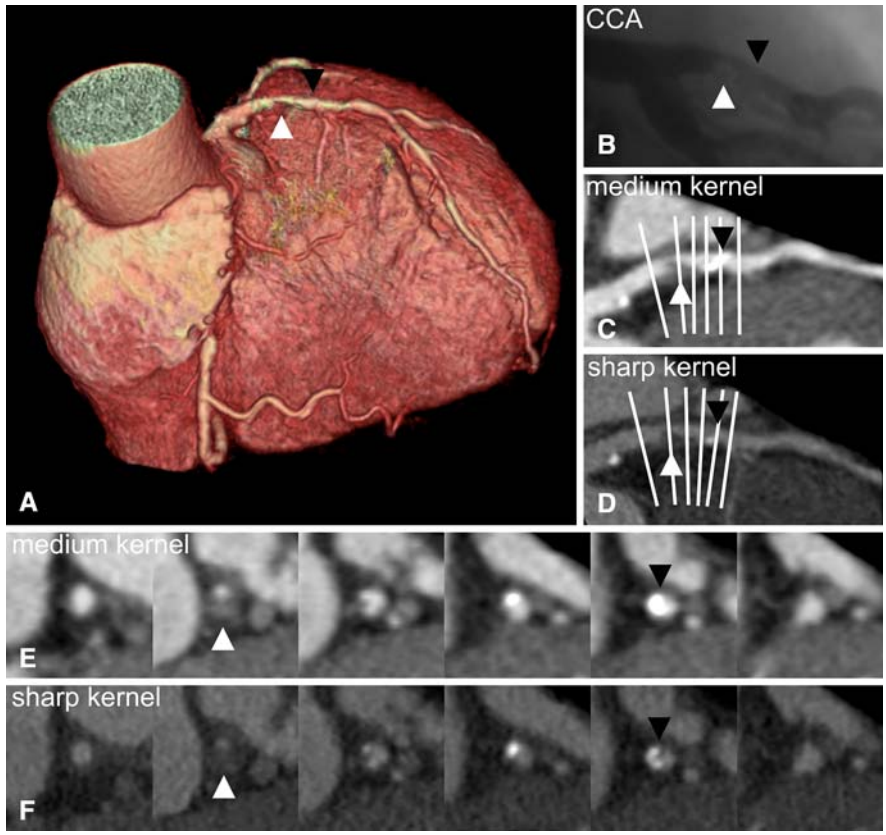

Fig. 2 Demonstration of a non-calcified, significant stenosis (*white arrow head*) and a sequential calcified, non-significant stenosis (black arrow head) with CTCA (**a**, **c**–**f**) and CCA (**b**) in a 72-year-old male, hypertensive patient. The volume rendered image (**a**) demonstrates the location of stenoses in the proximal LAD after removal of left atrial appendage, the pulmonary trunk, and parts of the right ventricle. The CCA-image (**b**) demonstrates one significant stenosis in the proximal LAD. CTCA curved multiplanar reconstructions with a medium tissue convolution kernel (**c**) and a sharp tissue convolution kernel (**d**) demonstrate the same stenosis and a sequential calcified lesion distal of the non-calcified stenosis; the white lines demonstrate planes, perpendicular to the course of the vessels, used for image reconstructions in **e** and **f**. Image **e** demonstrate the significant, non-calcified stenosis (*white arrow head*) and the calcified lesion with blooming artifact (*black arrow head*). With the use of a sharp tissue convolution kernel (**f**) the artifact appears less severe using bone-window setting

significantly differ to normotensive patients, despite more calcifications in hypertensives. CTCA is a useful tool to accurately rule out CAD in hypertensives and should therefore be considered as a valuable non-invasive alternative to prevent unnecessary CCA in this population.

Conclusion

Although hypertensives have significantly higher coronary calcifications, sensitivity and specificity are comparably high as in normotensives. The prevalence of CAD is higher in hypertensives and brings about a trend towards a lower NPV and a higher PPV.

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